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Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg)

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ABSTRACT

Objectives To examine whether pregnancy loss (miscarriage, abortion or stillbirth) is associated with a higher risk of myocardial infarction (MI) and stroke.

Design Population-based prospective cohort study.

Setting The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Heidelberg, Germany (mean follow-up 10.8 years).

Participants All 11 518 women who had ever been pregnant (aged 35–66).

Results Out of the participants, 2876 (25%) had at least one miscarriage, 2053 (18%) had at least one abortion and 209 (2%) had at least one stillbirth. During the follow-up, 82 cases of MI and 112 of stroke (confirmed by medical records) occurred in these women. Each stillbirth increased the risk of MI 2.65 times (95% CI for age-adjusted HR 1.37 to 5.12; HR adjusted for age, smoking, alcohol consumption, body mass index, waist to hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidaemia and diabetes mellitus: HR 2.32 95% CI 1.19 to 4.50, 95% CI). Recurrent miscarriage (>3) was associated with about nine times higher risk of MI (age-adjusted HR=8.90, 95% CI 3.18 to 24.90; fully adjusted HR 5.06, 95% CI 1.26 to 20.29). No significant association was found between abortion and MI or between any type of pregnancy loss and stroke.

Conclusions These results suggest that women who experience spontaneous pregnancy loss are at a substantially higher risk of MI later in life. Recurrent miscarriage and stillbirth are strong sex-specific predictors for MI and thus should be considered as important indicators for cardiovascular risk factors monitoring and preventive measures. Further research is suggested to elucidate underlying risk factors of pregnancy loss that at the same time strongly predispose to cardiovascular disease.

INTRODUCTION

Metabolic and hormonal changes associated with pregnancy may contribute to the development of cardiovascular disease (CVD). Studies that have examined pregnancy loss and subsequent risk of CVD have shown inconsistent results. Some have suggested that miscarriage and induced abortion may increase the risk,[1] but others have shown the increase only for miscarriage[2] but not abortion,[3] and some found no clear association for any kind of pregnancy loss.[4–6] Although miscarriage is the most common complication of pregnancy, occurring in 15–20% of ongoing pregnancies,[7] long-term effects of miscarriage on maternal health have received only modest attention. Given the importance of placental function for the risk of miscarriage, it may be speculated that women with a tendency for repeated miscarriages may also be at higher risk of vascular disease later in life. High maternal blood pressure has been considered to be one of the possible causes of stillbirth. Mothers with hypertensive disorders during pregnancy have a higher risk of stillbirth.[8 9] Stillbirths have been associated with an increased risk of atherosclerosis and coronary heart diseases.[10 11]

To further elucidate the association between pregnancy loss (miscarriage, abortion and stillbirth) and higher risk of cardiovascular health in women, we investigated this subject in the European Prospective Investigation into Cancer and Nutrition (EPIC)—Heidelberg cohort.

MATERIAL AND METHODS

Study population

EPIC in Heidelberg is a prospective cohort aiming at the investigation of the association between diet, lifestyle and chronic diseases, with emphasis on cancer. At recruitment (1994–8), information on diet, anthropometry, lifestyle, health status, medication, reproductive history, physical activity, socioeconomic status, blood pressure measurement and blood sample were collected from 11 928 men and 13 612 women, aged 35–65 years at recruitment, who were from the general population, residing in Heidelberg (Germany) and surrounding communities.[12] The overall participation rate in women was 40%. Selection factors of the cohort recruitment are described in details elsewhere.[13] Briefly, comparison with the reference population showed that more women with higher educational level were included in the study. Additionally, the proportion of smokers and ex-smokers was higher and the frequency of obesity was lower than in the total population.

Every 2–3 years, a follow-up questionnaire is mailed to the study participants. The follow-up questionnaires are the major source of information for outcome ascertainment and for updates on specific exposures or risk factors. In this study, we used data from the baseline and four rounds of follow-up. The informed consent signed by the participants included an agreement for an analysis of non-cancer diseases. The study protocol was approved by the responsible local ethics committee.

Our exposures of interest (pregnancy loss) were assessed by self-administered questionnaire at baseline. The subjects replied to the questionnaire's questions: "Have you ever had a miscarriage/abortion/stillbirth?"; if yes, "How many times?"

Outcomes of interest (myocardial infarction (MI) and stroke) were obtained from record linkage to hospital discharge, death certificate and/or self-report during four rounds of follow-up. Self-reported and hospital discharge cases were verified by medical records (ECG and enzymatic measurements) by a doctor. Of 13 612 women aged 35–66 (mean 49.8), 11 518 had ever been pregnant, and therefore had the possibility of having history of pregnancy loss. During the follow-up, 82 cases of MI and 112 of stroke (confirmed by medical records) occurred in these women. Out of them, those who had no history of MI at baseline were included in this study (10 972 MI-free women and 79 MI cases; those with unconfirmed information on MI were excluded from the analyses). International Classification of Disease (ICD-10) codes I21.0 to I21.4 and I21.9 were used for MI.

We also assessed the association of pregnancy loss and stroke in ever-pregnant women, with no history of stroke at baseline (10 959 stroke-free women and 107 stroke cases; those with unconfirmed information on stroke were excluded from the analyses). ICD-10 codes I60.0 to I62.9 were used for haemorrhagic stroke (28 cases) and codes I63.0 to I63.9 were used for ischaemic stroke (66 cases) and code I64 for unspecified stroke (18 cases).

Covariates

Formal education was categorised as none or primary school completed, technical or professional school, secondary school and university degree. Participants were categorised as non-smokers, ex-smokers or current smokers. Education, smoking and leisure time physical activity (classified as inactive, moderately inactive, moderately active and active based on Cambridge questionnaire[14]) were assessed by questionnaire at baseline. Alcohol consumption was calculated based on the data collected with a self-administered and validated food frequency questionnaire at baseline. Diabetes mellitus, hyperlipidaemia and hypertension were based on self-reported information at baseline. Height, weight and waist to hip ratio were obtained from direct examination at baseline. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). A few outlier values for anthropometric variables such as waist or hip circumferences were replaced with a missing value.

Statistical analyses

Associations between miscarriage, abortion and stillbirth and subjects' baseline characteristics were evaluated using a χ^2 test or linear regression. The SAS procedure PHREG (Cox proportional hazard models) was used to estimate hazard ratios (HR)s and 95% CIs of MI and stroke for pregnancy loss (miscarriage, abortion and stillbirth). In all the analyses, age was used as an underlying time variable, with entry time defined as the subject's age at recruitment and exit time defined as age at MI or stroke diagnosis or censoring (death, lost to follow-up or end of follow-up). All multivariable models were stratified by age at recruitment (in 1-year categories) to minimise the sensitivity against violations of the proportional hazard assumption.

In the 'fully adjusted' model, the following potential covariates were included: total number of previous pregnancies, history of hypertension, diabetes mellitus and hyperlipidaemia as reported at recruitment, smoking, alcohol consumption, BMI, waist to hip ratio, physical activity and education (as a proxy of socioeconomic status). The number of total pregnancies (including pregnancy loss), lifetime alcohol consumption (g/day), waist to hip ratio and BMI at baseline were used as continuous variables in the analyses. The analyses were repeated in a subgroup of women aged ≥49 at baseline. All analyses were done using SAS statistical software, version 9.2 (SAS Institute).

RESULTS

Among 11 518 women who had ever been pregnant, 2876 (25%) had at least one miscarriage, 2053 (18%) had at least one abortion and 209 (2%) had at least one stillbirth. Women with history of miscarriage more often had a history of either past or current smoking and had a slightly higher waist to hip ratio (table 1). Among 2876 women who had experienced miscarriage, 69 had experienced more than three miscarriages (recurrent miscarriage). These women had higher BMI and waist to hip ratio than other women. Women with a history of abortion were younger, more often an ever-smoker and more physically active, had higher educational level and less often had diabetes mellitus, hyperlipidaemia or hypertension than women who had never had abortion. They were also taller and had lower BMI and waist to hip ratio. Women with history of stillbirth, by contrast, were significantly older, less educated and physically less active and more often reported diabetes mellitus, hyperlipidaemia, or hypertension than those had no history of stillbirth. These women with a history of stillbirth were also shorter and had higher BMI and waist to hip ratio.

During the follow-up (mean follow-up 10.8 years), 79 MI cases occurred in women who ever had been pregnant and had no history of MI at baseline. Risk of MI increased more than 40% with each miscarriage (age-adjusted HR=1.42, 95% CI 1.14 to 1.78; table 2). The increased risk was 4.34 times for those who had more than two miscarriages compared with those who reported none (95% CI 1.85 to 10.18). Recurrent miscarriage (>3) was associated with an approximately nine times higher risk of MI (age-adjusted HR=8.90, 95% CI 3.18 to 24.90). After adjustment for smoking, alcohol consumption, BMI, waist to hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidaemia and diabetes mellitus, this association remained significant (fully adjusted HR 5.06 95% CI 1.29 to 20.29). History of having stillbirth was associated with more than 3.5 times higher risk of MI (age-adjusted HR 3.70, 95% CI 1.69 to 8.11 fully adjusted HR 3.43, 95% CI 1.53 to 7.72). No significant association was found between history of induced abortion and MI.

During the follow-up, 107 cases of stroke occurred in women with history of pregnancy and without previous history of stroke at baseline. No significant association was found between history of miscarriage, abortion or stillbirth and the risk of stroke (table 2). Owing to the small number of stroke cases in each subgroup, we could not conduct subgroup analysis for haemorrhagic and ischaemic stroke.

When restricting the analyses to women aged ≥49 at recruitment (based on mean age at menopause in our sample; n=5882) who had little or no chance of further pregnancy, the association between recurrent miscarriage (>3) and MI did not change substantially (age-adjusted HR=9.07, 95% CI 3.23 to 25.45, fully adjusted HR=4.88, 95% CI 1.20 to 19.90). Nevertheless, no significant association was found between history of miscarriage, abortion or stillbirth and the risk of stroke (table 3).

DISCUSSION

History of recurrent miscarriage (>3) was associated with an approximately nine times higher risk of MI and history of stillbirth with more than three times higher risk of MI. We did not find any significant association between abortion and MI risk or pregnancy loss and stroke risk. Our results were in line

Table 1 Baseline data

	Miscarriage				Abortion			Stillbirth		
	0	1–3	>3		No	Yes		No	Yes	
	n			p Value	n		p Value	n		p Value
Age group				0.358			<0.001			<0.001
35–44	2908	976	21		2965	951		3876	37	
45–54	2972	910	23		3140	767		3853	59	
≥55	2731	911	25		3337	335		3560	113	
Missing	41				23			20		
Education				<0.001			<0.001			<0.001
None/primary school completed	2516	801	20		3001	340		3249	92	
Technical/professional school	3539	1064	31		3934	703		4557	82	
Secondary school	690	217	5		667	248		911	4	
University degree	1864	714	13		1837	762		2569	31	
Missing	44				26			23		
Alcohol drinking				0.971			0.009			0.192
Never	211	71	1		247	37		276	8	
Former drinker	303	111	3		352	65		409	9	
Only current drinker	116	34	1		136	15		145	6	
Past and current drinker	7979	2581	64		8705	1936		10457	186	
Missing	43				25			22		
Smoking				0.010			<0.001			0.997
Never	4259	1283	31		4859	728		5485	101	
Former	2441	878	20		2633	709		3284	61	
Current	1911	636	18		1950	616		2520	47	
Missing	41				23			20		
Physical activity				0.149			0.028			0.019
Inactive	1029	367	8		1163	243		1369	39	
Moderately inactive	3057	1023	26		3408	705		4033	78	
Moderately active	2465	799	15		2711	572		3233	52	
Active	2059	608	20		2159	533		2653	40	
Missing	42				24			21		
Diabetes mellitus				0.910			<0.001			<0.001
No	8390	2719	67		9168	2024		11000	195	
Yes	211	73	2		263	25		274	14	
Missing	56				38			35		
Hyperlipidaemia				0.164			<0.001			0.010
No	6024	1956	41		6506	1525		7905	129	
Yes	2587	841	28		2936	528		3384	80	
Missing	41				23			20		
Hypertension				0.054			<0.001			<0.001
No	6389	2096	43		6900	1643		8412	131	
Yes	2222	701	26		2542	410		2877	78	
Missing	41				23			20		
	Mean (SD), range, and missing				Mean (SD), range and missing			Mean (SD), range and missing		
Height (cm)										
Mean (SD)	163.70 (6.21)	163.58 (6.26)	162.16 (5.69)	0.152	163.47 (6.20)	164.55 (6.29)	<0.001	163.70 (6.22)	161.40 (6.08)	<0.001
Range	135.7–198.0	138.0–188.5	147.8–178.0		135.7–198.0	135.8–185.5		135.7–198.0	143.6–188.3	
Missing	41									
Weight (kg)										
Mean (SD)	68.46 (12.48)	68.43 (12.56)	69.84 (10.65)	0.889	68.87 (12.59)	66.59 (11.81)	<0.001	68.45 (12.49)	69.22 (12.66)	0.374
Range	29.3–149.8	42.8–152.0	48.9–94.0		29.3–152.0	42.8–140.0		29.3–152.0	47.1–114.4	
Missing (n)	41									
Body mass index (kg/m^2)										
Mean (SD)	25.46 (4.60)	25.48 (4.62)	26.36 (4.53)	0.558	25.81 (4.65)	24.46 (4.28)	<0.001	25.45 (4.60)	26.73 (4.83)	<0.001
Range	16.0–48.4	16.7–48.4	18.1–38.6		16.0–54.2	16.5-49.7		16.0–54.2	18.8–42.9	
Missing (n)	41									
Waist to hip ratio										
Mean (SD)	0.80 (0.06)	0.81 (0.07)	0.82 (0.07)	0.025	0.81 (0.07)	0.79 (0.06)	<0.001	0.81 (0.7)	0.82 (0.07)	<0.001
Range	0.5–1.3	0.6–1.4	0.7–1.1		0.5–1.4	0.5–1.1		0.5–1.4	0.7–1.1	
Missing (n)	41									

Table 2 Pregnancy loss and risk of myocardial infarction

	Myocardial infarction																			
	No	Yes	Age-adjusted		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	n	n	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Miscarriage																
Continuous			**1.42**	1.14 to 1.78	1.25	0.94 to 1.65	1.23	0.93 to 1.63	1.26	0.94 to 1.69	1.27	0.95 to 1.71	1.27	0.94 to 1.70	1.27	0.95 to 1.70
No	8216	53	1.00													
Yes	2725	26	1.42	0.88 to 2.30	1.07	0.63 to 1.82	1.04	0.61 to 1.76	1.16	0.67 to 2.00	1.19	0.69 to 2.05	1.18	0.69 to 2.04	1.18	0.69 to 2.04
1–3 versus 0	2656	22	1.23	0.74 to 2.04	1.02	0.59 to 1.77	0.98	0.56 to 1.70	1.12	0.64 to 1.96	1.14	0.65 to 2.00	1.14	0.65 to 2.00	1.14	0.65 to 1.99
>3 versus 0	59	4	**8.90**	3.18 to 24.90	**5.01**	1.45 to 17.33	**4.98**	1.43 to 17.29	**4.75**	1.19 to 19.05	**4.93**	1.22 to 19.86	**4.98**	1.24 to 20.04	**5.06**	1.26 to 20.29
Abortion																
Continuous			1.05	0.70 to 1.57	0.83	0.54 to 1.27	0.82	0.54 to 1.26	0.87	0.57 to 1.31	0.86	0.57 to 1.30	0.86	0.57 to 1.30	0.86	0.57 to 1.29
No	9011	69														
Yes	1938	10	1.11	0.55 to 2.26	0.80	0.38 to 1.72	0.77	0.37 to 1.64	0.88	0.41 to 1.89	0.87	0.41 to 1.87	0.88	0.41 to 1.89	0.87	0.41 to 1.88
1–3 versus 0	1880	10	1.17	0.57 to 2.37	0.87	0.41 to 1.84	0.84	0.40 to 1.76	0.96	0.45 to 2.04	0.95	0.45 to 2.02	0.96	0.45 to 2.04	0.96	0.45 to 2.04
>3 versus 0	53	0	NC		NC		NC		NC		NC		NC		NC	
Stillbirth																
Continuous			**2.65**	1.37 to 5.12	**2.15**	1.08 to 4.26	**2.05**	1.05 to 4.01	**2.24**	1.16 to 4.31	**2.39**	1.23 to 4.67	**2.39**	1.23 to 4.64	**2.32**	1.19 to 4.50
No	10 762	72														
Yes	190	7	**3.70**	1.69 to 8.11	**2.91**	1.30 to 6.53	**2.88**	1.28 to 6.47	**3.42**	1.52 to 7.71	**3.46**	1.54 to 7.78	**3.49**	1.55 to 7.84	**3.43**	1.53 to 7.72

Model 1: Adjusted for age, total number of pregnancies and education.
Model 2: Adjusted for above-mentioned variables plus smoking, alcohol and physical activity.
Model 3: Adjusted for variables in models 1 and 2 plus body mass index and waist to hip ratio.
Model 4: Adjusted for variables in models 1, 2 and 3 plus hypertension.
Model 5: Adjusted for all above-mentioned variables plus diabetes mellitus.
Model 6: Adjusted for above-mentioned variables plus hyperlipidaemia.
Bold HR, statistically significant.
HR, hazard ratio; NC, not calculable.

with those from a prospective study in Scotland, in which women with a history of spontaneous loss of early pregnancy were also observed to be at increased risk of heart disease, but those who had had abortion were not.[3] That study which is the largest scale and highest quality study of the association between miscarriage and subsequent ischaemic heart disease by far, suffered from lack of information on potential confounders such as smoking. This issue was also assessed in a nationally representative sample comprising 3937 Finnish women aged 30–99 years. Age, smoking, body mass index, waist to hip ratio, physical activity, education, number of previous pregnancies, blood pressure and fasting blood glucose and cholesterol as potentially confounding factors were considered in that study. In Finnish women (aged 50–74) who had experienced pregnancy, history of miscarriage was associated with about twofold increase in the odds of MI and the odds increased significantly with the number of miscarriages.[2] However, owing to the cross-sectional design of that study, no inferences on causality could

Table 3 Pregnancy loss and risk of stroke

	Stroke															
	No	Yes	Age-adjusted		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	n	n	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Miscarriage																
Continuous			0.92	0.67 to 1.25	0.87	0.61 to 1.22	0.86	0.61 to 1.22	0.90	0.63 to 1.29	0.91	0.64 to 1.29	0.91	0.64 to 1.29	0.91	0.64 to 1.29
No	8196	86														
Yes	2733	21	0.75	0.46 to 1.23	0.69	0.40 to 1.18	0.68	0.40 to 1.16	0.71	0.41 to 1.23	0.72	0.42 to 1.25	0.72	0.42 to 1.25	0.72	0.42 to 1.25
1–3 versus 0	2663	20	0.74	0.45 to 1.21	0.68	0.45 to 1.21	0.67	0.39 to 1.15	0.70	0.40 to 1.23	0.70	0.40 to 1.23	0.72	0.41 to 1.25	0.72	0.41 to 1.25
>3 versus 0	60	1	1.66	0.23 to 11.97	1.29	0.16 to 10.44	1.28	0.16 to 10.29	1.34	0.17 to 10.95	1.34	0.17 to 10.95	1.30	0.16 to 10.64	1.31	0.161 to 0.65
Abortion																
Continuous			1.12	0.82 to 1.54	1.12	0.79 to 1.60	1.10	0.78 to 1.56	1.14	0.80 to 1.61	1.13	0.80 to 1.60	1.14	0.81 to 1.61	1.14	0.81 to 1.61
No	9001	90														
Yes	1936	17	1.26	0.73 to 2.18	1.27	0.71 to 2.26	1.22	0.68 to 2.17	1.32	0.73 to 2.37	1.33	0.74 to 2.39	1.34	0.74 to 2.40	1.33	0.74 to 2.40
1–3 versus 0	1880	16	1.22	0.70 to 2.14	1.24	0.69 to 2.24	1.19	0.66 to 2.15	1.29	0.71 to 2.35	1.30	0.72 to 2.37	1.31	0.72 to 2.38	1.31	0.72 to 2.38
>3 versus 0	50	1	2.71	0.38 to 19.61	2.81	0.34 to 22.90	2.57	0.32 to 20.60	2.70	0.33 to 21.84	2.69	0.33 to 21.85	2.76	0.34 to 22.42	2.73	0.34 to 22.27
Stillbirth																
Continuous			1.62	0.65 to 4.07	1.59	0.62 to 4.03	1.47	0.58 to 3.74	1.57	0.63 to 3.93	1.57	0.62 to 4.02	1.57	0.62 to 4.00	1.57	0.62 to 3.99
No	10 748	102														
Yes	192	5	1.87	0.69 to 5.12	1.83	0.66 to 5.10	1.70	0.61 to 4.74	1.89	0.68 to 5.28	1.81	0.65 to 5.05	1.82	0.65 to 5.06	1.81	0.65 to 5.05

Model 1: Adjusted for age, total number of pregnancies and education.
Model 2: Adjusted for above-mentioned variables plus smoking, alcohol and physical activity.
Model 3: Adjusted for variables in models 1 and 2 plus body mass index and waist to hip ratio.
Model 4: Adjusted for variables in models 1, 2 and 3 plus hypertension.
Model 5: Adjusted for all above-mentioned variables plus diabetes mellitus.
Model 6: Adjusted for above-mentioned variables plus hyperlipidaemia.
HR, hazard ratio.

be drawn. Our results were based on a cohort study and independent of confounding factors such as smoking, alcohol consumption, body mass index, waist to hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidaemia and diabetes mellitus.

It is widely believed that oestrogen protects women from CVD. However, it is not known whether reproductive history, which affects endogenous oestrogen levels during a woman's life, also influences CVD risk.[1] Since it is known that pregnancy duration influences the length of time a woman is exposed to a higher oestrogen level in her premenopausal life, a pregnancy ending in an abortion, miscarriage or stillbirth would expose a woman to a lower level of oestrogen than a full-term pregnancy. On the other hand, pregnancy loss results in an increasing number of total pregnancies to achieve the required family size. Therefore, to assess this topic, we also considered the possible role of the total number of pregnancies in these associations and the results that we presented for pregnancy loss and CVD, were independent of the total number of pregnancies.

Owing to the wide CI of our non-significant results for stroke, these results are inconclusive. This might be because the association was limited to a specific subgroup (ischaemic stroke). However, owing to the small number of cases in each category of stroke (ischaemic, haemorrhagic and unknown), a subgroup analysis was not possible and needs to be confirmed in larger sample. Smith *et al*[15] found that previous spontaneous abortions (adjusted HR=1.49, 95% CI 1.09 to 2.03) were predictive of subsequent maternal cerebrovascular events (ICD-10 codes I60–I69). Their results were not significant in the multivariable analyses of more specific end points for stroke subtypes (ischaemic and haemorrhagic). The only significant independent predictor of transient ischaemic attacks was previous spontaneous abortion (adjusted HR=2.7, 95% CI 1.07 to 4.02). We included only stroke cases (ICD-10 codes I60–I64) and not transient ischaemic attack and other cerebrovascular events in our study and in line with their results we found no significant association between stroke and spontaneous miscarriage, although women who had history of recurrent miscarriage (>3) tended to have a higher risk of stroke (adjusted HR=1.43, 95% CI 0.17 to 11.78). The subgroup analysis of stroke (haemorrhagic/ischaemic) was not possible in our current sample owing to small sample size in each subgroup of stroke.

Combining our results with earlier findings which show that mothers with hypertensive disorders during pregnancy have a higher risk of stillbirth,[8 9] we infer that stillbirth is an outcome due to the underlying risk factors of CVD (for instance, hypertension) in mothers rather than a causative risk factor for CVD. Hypertension and diabetes have been shown to be responsible for a significant proportion of fetal deaths. The most prevalent risk factor for stillbirth after late maternal age and low socioeconomic status is pre-pregnancy obesity.[16] On the other hand, maternal obesity is associated with hyperlipidaemia and clinically significant atherosclerosis.[17] However, our results were adjusted for obesity indices (BMI and waist to hip ratio).

Our findings have a great deal of biological plausibility as many of the medical conditions that predispose to miscarriage and stillbirth can also predispose towards heart diseases. A study on a mouse model showed that those mice with recurrent miscarriages had high levels of tissue factor (TF), a protein that promotes inflammation and clotting.[18] They found that pravastatin (a statin drug that is also used to prevent clotting and inflammation within the cardiovascular system) diminished TF levels, prevented thrombosis and restored placental blood flow. This study also indicated that TF is an important mediator in fetal death and that statins may be a good treatment for women with recurrent miscarriages.

Antiphospholipid antibodies (aPL) may lead to complications such as stroke, heart attack and miscarriage. Fetal loss in patients with aPL has been ascribed to thrombosis of placental vessels. However, Redecha *et al* have shown that inflammation is an essential trigger of fetal injury.[19] They analysed the role of the procoagulant molecule TF in a mouse model of aPL-induced pregnancy loss. The identification of TF as an important mediator of inflammation in aPL-induced fetal injury provides a new target for treatment to prevent pregnancy loss in the antiphospholipid syndrome.

Miscarriage can sometimes lead to infections which may also have some links with CVD. For instance, Chlamydia infection has been found to be associated with occurrence of miscarriage.[20] Macrophages infected with Chlamydia have altered membrane physicochemical characteristics which may render them atherogenic.[21] Inflammation and infection as known risk factors for CVD might be the underlying mechanisms that explain the association between miscarriage and CVD.

A study suggests the endothelial dysfunction as a link between pre-eclampsia, recurrent pregnancy loss and future cardiovascular events.[22] Endothelial dysfunction could cause placentation-related defects, persist after the complicated pregnancy and probably cause CVD later in life. Endothelial dysfunction may represent a link between pre-eclampsia and increased CVD later in life and might explain the fact that women with unexplained recurrent miscarriages are also at increased CVD risk. The effect of identification and correction of endothelial dysfunction detected during the reproductive stage on obstetric outcome and on CVDs still needs to be elucidated.

High homocysteine levels in early pregnancy are another risk factor for pregnancy loss and pre-ecclampsia.[23] Elevated levels of homocysteine in the bloodstream can irritate the blood vessels, which may eventually lead to hardening of the arteries, stroke or heart attack. The increased risk of CVD associated with miscarriage might therefore be partly mediated with high homocysteine levels.

What is already known on this topic

- A few cross-sectional studies and only one prospective study with incomplete adjustment for confounding factors (such as smoking and diabetes mellitus) have shown inconsistent results for the association of pregnancy loss and subsequent risk of cardiovascular disease

What this study adds

- Our population-based cohort study showed that women who experience spontaneous pregnancy loss are at a substantially higher risk of myocardial infarction later in life independent of the known risk factors of cardiovascular diseases.
- Recurrent miscarriage and stillbirth are strong sex-specific predictors for myocardial infarction and thus should be considered as important indicators for monitoring of cardiovascular risk factors and preventive measures.

Our study was prospective and the associations we found were independent of age, smoking, alcohol consumption, body mass index, waist to hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidaemia and diabetes mellitus. However, possible effects of residual confounding should be considered. About half of the subjects who had no history of miscarriage at baseline were below the mean menopausal age (49 years) and our data on reproductive history (miscarriage, abortion, stillbirth and total number of pregnancy) were obtained at baseline. Furthermore, the length of follow-up (mean 10.8 years) was not sufficient for occurrence of our outcomes of interest in subjects who were aged 35–50 years at recruitment. Therefore, we repeated our analyses on the subgroup of women aged ≥49 years at recruitment. In the subgroup analyses, the association between recurrent miscarriage (>3) and MI did not change substantially and still no significant association was found between history of miscarriage, abortion or stillbirth and the risk of stroke.

The major strengths of our study are the prospective design, the relatively large sample size, active follow-ups with verified outcome assessment by a doctor, almost 90% completeness of follow-ups, the information available on the most relevant potentially confounding factors and recruitment of subjects from the general population. The participation of more educated subjects, more current smokers and less obese subjects than in the underlying population,[13] might have resulted in over-estimation of current smoking and underestimation of the educational level and obesity in our subjects. Miscarriages were more probably under-reported. In some cases, women do not even realise that they have been pregnant and that a spontaneous abortion has occurred. However, any recall error for miscarriage should be non-differential with regard to our outcome variables (MI or stroke) as we assessed the exposures before the occurrence of the outcomes of interest.

These results suggest that women who experienced spontaneous pregnancy loss are at a substantially higher risk of MI later in life. Recurrent miscarriage and stillbirth are strong sex-specific predictors for MI and thus should be considered as important indicators for monitoring cardiovascular risk factors and preventive measures. Pregnancy loss and CVD seem to share common risk factors. Further research is suggested to elucidate underlying risk factors of pregnancy loss that at the same time strongly predispose to CVDs.

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Competing interests None.

Patient consent Obtained. The informed consent signed by the participants included an agreement for an analysis of non-cancer diseases.

Ethical approval The general cohort study protocol was approved by the responsible local ethics committee. Separate ethical approval was not required.

Contributors EK: conception and design, data analysis and interpretation, manuscript writing and final approval of manuscript. LD: consultation for data analysis, commented on the manuscript. SR: administrative support and commented on the manuscript. RK: financial support, administrative support, provision of study material, commented on the manuscript and final approval of the manuscript. Name of the guarantor: Professor Rudolf Kaaks

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